Beating the Clock in T-cell Acute Lymphoblastic Leukemia

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CDK4/6 inhibition was synergistic with dexamethasone and everolimus but antagonistic with conventional chemotherapy in T-cell acute lymphoblastic leukemia (T-ALL) preclinical models. Cyclin-dependent kinase inhibition in combination with glucocorticoids and mTOR inhibition offers a unique therapeutic opportunity in T-ALL. Clin Cancer Res; 23(4); 873–5.

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See related article by Pikman et al., p. 1012

In this issue of Clinical Cancer Research, Pikman and colleagues demonstrate that T-cell acute lymphoblastic leukemia (T-ALL) cells are particularly vulnerable to cyclin-dependent kinase (CDK) inhibition, especially when given in combination with dexamethasone and everolimus (1). Optimal cell-cycle regulation is a prerequisite for normal cell proliferation and differentiation. Normal cells divide only when needed and exit the cell cycle under the control of a variety of external cues. Thus, it is not surprising that hallmarks of cancer are molecular aberrations that disrupt the "cell-cycle clock," leading to unrestrained proliferation and failure to differentiate or exit into the quiescent state. The cell cycle is divided into G1 (pre-DNA synthesis), S (DNA synthesis), G2 (predivision), and M (cell division) phases (Fig. 1). These sequential phases are largely guided by cyclins and CDKs. Human cells contain 20 CDKs and 29 cyclins that participate in a wide variety of cell processes, including cell-cycle control, DNA repair, and transcription. Upon mitogenic stimulation, cyclins engage CDKs, leading to their activation. Although CDK expression is relatively constant throughout the cell cycle, the levels of various cyclins oscillate, thereby controlling the consecutive orchestration of cell-cycle progression.

The G1 phase of the cell cycle is particularly responsive to extracellular mitogens and inhibitory proteins. The cyclin D–CDK4/6–Rb pathway is a key regulator of the G1→S transition. D-type cyclins associate with either CDK4 or CDK6 (they share extensive homology), and these active complexes phosphorylate the tumor suppressor Rb protein, leading its release from Rb–E2F complexes to repress transcription at key target genes. This frees E2F to activate genes involved in the S-phase entry and DNA replication. CDK4/6 activity is negatively regulated by the INK4 family of proteins, particularly p16INK4A (CDKN2A) but also p21cip1 and p27kip1, among other proteins. Cancer cells frequently contain gain-of-function or loss-of-function defects that either directly activate the pathway (e.g., cyclin D amplification and/or overexpression), upregulate mitogenic signals that converge on cyclin D–CDK4/6 (e.g., PI3K/AKT/mTOR, MAPK, and other pathways), or indirectly activate the pathway through loss of negative regulators (e.g., deletion of CDKN2A locus).

As molecular aberrations associated with the cyclin–CDK pathway appear to be oncogenic drivers, inhibition of these pathways might expose unique vulnerabilities. Indeed, since the 1990s, a number of CDK inhibitors have been developed, the first of which was flavopiridol (2). Although the compound showed clinical activity, its broad CDK inhibition resulted in significant toxicity. More recently, second-generation CDK inhibitors have been developed with far greater specificity. Currently, there are three CDK4/6 inhibitors in late-stage clinical trials: palbociclib (PD-0332991; Pfizer), ribociclib (LEE011; Novartis), and abemaciclib (LY2835219; Eli Lilly; ref. 3). All of these compounds are selective cyclin D–CDK 4/6 inhibitors, but there are subtle differences in pharmacokinetic and pharmacodynamic properties. These compounds have shown significant activity in solid tumors, but their greatest impact has been in combination with other drugs, particularly in combination with hormonal therapy in hormone receptor–positive breast cancer. Those cancers that show activation of the cyclin D–CDK4/6–Rb pathway might be particularly sensitive to CDK4/6 inhibition. Retention of a functional Rb pathway is a prerequisite for activity.

Pikman and colleagues demonstrated significant preclinical activity of ribociclib (LEE011) in T-ALL (1). The authors were quite justified in considering T-ALL as an attractive candidate for CDK inhibition. Previously, it had been shown that cyclin D3 expression is essential for induction of T-ALL in a NOTCH1-driven murine model, and subsequent studies showed that CDK4/6 inhibition halted proliferation of human T-ALL cell lines and significantly improved survival in a xenograft model (4, 5). Moreover, cyclin D3 expression is upregulated in T-ALL, presumably through NOTCH1 activation, and the majority (70%) of T-ALL samples show loss of the CDKN2A/B locus (6). These data suggest that cyclin D–CDK4/6 inhibition could represent a novel therapeutic approach in T-ALL and T lymphoblastic lymphoma. Indeed, novel therapies are needed for this disease. Although the outcome for childhood T-ALL has improved considerably, patients still require more dose-intensive regimens compared with their more common B-ALL counterpart, and relapsed T-ALL

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has a dismal prognosis. Also, the outcome for adults is inferior to that achieved in children.

In many cases, CDK4/6 inhibition is cytostatic, and, therefore, monotherapy is unlikely to be optimal. Pikman and colleagues used ribociclib in combination with drugs relevant to T-ALL, including conventional agents. They showed that CDK4/6 inhibition was antagonistic when given simultaneously with conventional cytotoxic agents (1). This result may not be surprising as G1–S arrest would make cells less vulnerable to cell-cycle–specific agents. However, other preclinical and clinical results are conflicting about the impact of simultaneous administration. Sequential administration of ribociclib and chemotherapy did not eradicate the antagonism. However, temporary exposure to a CDK4/6 inhibitor to induce cell-cycle arrest, followed by washout to allow synchronous S-phase entry, may increase the vulnerability of cells to cell-cycle–targeted agents (7). In addition, prolonged G1 arrest induced by CDK4/6 inhibition has been shown to alter gene expression, including components of the apoptotic pathway, in other cell-cycle phases after release of G1 arrest (8). Therefore, the jury is still out on combination CDK4/6 inhibition with conventional chemotherapy.

Pikman and colleagues showed that combination therapy with dexamethasone and the mTOR inhibitor everolimus resulted in a synergistic decrease in active proliferation and apoptosis of T-ALL cell lines and significantly extended survival in a xenograft model (1). mTOR inhibition is a rational combination strategy, since as mentioned, the PI3K/AKT/mTOR pathway targets cyclin D–CDK4/6 signaling, and a number of clinical trials are exploring combination therapy in breast cancer, using CDK4/6 inhibitors with endocrine therapy and an inhibitor of the PI3K/AKT/mTOR pathway. The impact of combination dexamethasone and ribociclib was likewise synergistic, although not as impressive in vitro (1). Glucocorticoids have been shown to decrease CDK4 expression in chronic lymphocytic leukemia cells (9), although something similar was not seen in the study by Pikman and colleagues. The authors are now poised to test their provocative results in a clinical trial for T-ALL. However, better therapy is also needed for the more common B-ALL. The authors reported results from The Genomics of Drug Sensitivity in Cancer Project, showing that many B-ALLs are also sensitive to CDK4/6 inhibition, although this did not quite meet statistical significance (1). Although not as prevalent as in T-ALL, the CDK2A/B locus is deleted in a third of B-ALLs.

Finally, there are other logical candidates for combination therapy, including RAS/RAF/MEK/ERK inhibitors. RAS pathway mutations are frequent in both T- (67% of early T-cell precursor ALL and 22% T-ALL) and B-ALL (35% at diagnosis and enriched at relapse; ref. 10). MAPK activation, even in the absence of known RAS mutations, is acquired at relapse and is associated with drug resistance (11). The association of resistance to BRAF-targeted therapy in melanoma cell lines and animal models with MAPK activation has led to clinical trials exploring doublet therapy in NRAS-mutant melanoma (12).

The article by Pikman and colleagues shows substantial opportunities for CDK4/6 inhibition in T-ALL and possibly other hematologic malignancies (1). The challenge will be to validate efficacy in the pediatric population given the small numbers of patients and the difficulty integrating therapy into heavily pretreated patients. Therefore, combining adult and pediatric populations and possibly including both B- and T-ALL may offer advantages.

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No potential conflicts of interest were disclosed.

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References
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